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# LANTUS SOLOSTAR IN REAL LIFE MEDICAL PRACTICE

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on behalf of the START trial investigators

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## Abstract

***Background and aims:*** *The epidemic of diabetes mellitus has made the effective treatment of hyperglycemia a top priority. Maintaining near-normal glycemic levels has been demonstrated to have a beneficial effect on diabetes-specific complications. Insulin can decrease any level of elevated glycated hemoglobin. Insulin glargine (Lantus®) is a long-acting insulin analog with a favorable 24-h time-action profile, once daily administration and low risk of hypoglycemia used in type 1 and 2 diabetes. In Romania, real-life data about glycaemic control is lacking.* ***Material and methods:*** *We present results from a retrospective, open-label, non-randomised, registry trial in 2946 Romanian diabetes patients. The objective of the study was to assess the proportion of patients with appropriate glycaemic control after 3 to 6 months of glargine treatment.* ***Results and conclusions:*** *A little over one third of the patients had reached target glycated hemoglobin after 3-6 months of glargine treatment in both types of diabetes. In type 2 diabetes patients the glargine dose used was not high (0.33 UI/kg). Inadequate insulin titration is a possible cause for not reaching glycemic targets.*

**key words**: *diabetes, insulin treatment, insulin glargine, real-life clinical practice.*

## Background and aims

The epidemic of diabetes mellitus and the recognition that achieving specific glycemic goals can substantially reduce complications have made the effective treatment of hyperglycemia a top priority. Maintaining glycemic levels as close to the nondiabetic range as possible has been demonstrated to have a powerful beneficial effect on diabetes-specific microvascular complications, including retinopathy, diabetic renal disease and neuropathy, in the setting of type 1 diabetes. In type 2 diabetes, more intensive treatment strategies have likewise been demonstrated to reduce microvascular complications [1].

Several randomized controlled trials (RCTs) have demonstrated the effects of improved glycemic control on diabetes-related complications. The landmark RCTs include two studies in patients with type 1 diabetes - the Diabetes Control and Complications Trial (DCCT) and the Stockholm Diabetes Intervention Study (SDIS) - and two studies in patients with type 2 diabetes - the U.K. Prospective Diabetes Study (UKPDS) and the Kumamoto Study [2].

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The American Diabetes Association's (ADA) 'Standards of Medical Care in Diabetes' [3] recommends lowering A1c glycated hemoglobin (HbA1c) to <7.0% in most patients to reduce the incidence of microvascular disease. This can be achieved with a mean plasma glucose of about 150–160 mg/dl; ideally, fasting and pre-meal glucose should be maintained at <130 mg/dl and postprandial glucose at <180 mg/d [l]. More stringent HbA1c targets (e.g. 6.0-6.5%) might be considered in selected patients (young, short disease duration, long life expectancy, no significant cardiovascular disease) if this can be achieved without significant hypoglycemia or other adverse effects of treatment [4]. Conversely, less stringent HbA1c goals (e.g. 7.5-8.0%, or even slightly higher) are appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counseling and effective doses of multiple glucose-lowering agents, including insulin [4].

In order to achieve the proposed targets of glycemic control we have at our disposal several classes of glucose lowering agents. The practician choice of specific antihyperglycemic agents is based on their effectiveness in lowering glucose, extraglycemic effects that may reduce long-term complications, safety profile, tolerability, ease of use, and cost [1].

Insulin is the oldest of the currently available medications and, therefore, the treatment which we have the most clinical experience with. It is also the most effective in lowering glycaemia. Insulin can, when used in adequate doses, decrease any level of elevated HbA1c to, or close to, the therapeutic goal. Unlike the other blood glucose-lowering medications, there is no maximum dose of insulin beyond which a therapeutic effect will not occur. In some patients with type 2 diabetes, relatively large doses of insulin (≥1 UI/kg), as compared with those required to treat type 1 diabetes, may be necessary to overcome the insulin resistance and lower HbA1c to the target level [1].

Ideally, the principle of insulin use is attaining a glycemic profile as normal as possible without unacceptable weight gain or hypoglycemia. As initial therapy, unless the patient is markedly hyperglycemic and/or symptomatic, "basal" insulin alone is typically added [5]. Basal insulin provides relatively uniform insulin coverage throughout the day and/or night, mainly to control blood glucose by suppressing hepatic glucose production in between meals and during sleep. Either intermediate-acting (neutral protamine Hagedorn [NPH]) or long-acting (insulin glargine or insulin detemir) formulations may be used [5].

Despite the availability of many classes of glucose-lowering agents, the majority of patients with a longer duration of diabetes remain poorly controlled with oral agents, and use of insulin, which could improve glycemic control, is often long delayed and not aggressive enough. The reluctance to initiate insulin therapy seems partly due to its perceived complexity, the belief that insulin is not effective for type 2 diabetes and fear of hypoglycemia, which may be the greatest barrier [6].

The International Diabetes Management Practice Study (IDMPS) [7] proved that there is a chasm between guidelines and practice in Asia, Eastern Europe, and Latin America. Based on case records, only 20-30% of patients were at the HbA1c goal, whereas 7.5% of type 1 and 3.6% of type 2 diabetic patients attained three treatment goals [7]. Many physicians noted adequate glycemic control despite no availability of HbA1c measurements, whereas others

overestimated the proportions of patients at goal. In both diabetes types, although body weight-adjusted insulin doses were within recommended guidelines, neither doses nor regimens predicted glycemic control [7].

Insulin glargine is a long-acting insulin analog with a more favorable 24-h time-action profile (no pronounced peak) than intermediate-acting human insulin preparations [6], once daily administration and lower risk of hypoglycemia. SoloStar® is a relatively novel insulin device approved for the administration of insulin glargine (Lantus®). SoloStar® offers a higher maximum dose (80 UI) than many of the other insulin devices already available. Previous studies have demonstrated the dose accuracy, low injection force, and patient preference for SoloStar® versus other prefilled insulin pen devices [8].

Real-life data about glycaemic control in Romania is scarce. We have planned to evaluate the level of glycaemic control in people treated with a basal analogue in once daily administration using a performing injecting device. The purpose of this retrospective study was to assess the proportion of patients with appropriate glycaemic control (HbA1c<7.0%) after 3 to 6 months of Lantus® SoloStar® treatment and to identify what are the physician's options for glycaemic control improvement.

## Material and methods

Male or female patients, aged more than 18 years, with type 1 (T1DM) or type 2 diabetes (T2DM) were enrolled at 178 sites from large/medium size cities distributed all across Romania, between September 2009 and December 2010. Further inclusion criteria were: consecutive patients treated at least 3 to 6 months with insulin glargine and the availability of a HbA1c determination in the last month before inclusion. No exclusion criteria, except for hypersensitivity to insulin glargine or excipients, were used. The trial was conducted in accordance with the Declaration of Helsinki. Approval by institutional ethics committees was obtained for each participating site. All patients provided written informed consent before study entry.

This was a retrospective, non-controlled, open-label, non-randomised, non-interventional, product registry study. The protocol didn't interfere with the patient management, as decided between physician and patient. No restriction on pharmacological and other treatments and no interference with dosage regimens recommended by physicians were imposed.

Only one visit was scheduled for collecting retrospective data from the patients' files in T1DM and T2DM patients treated for 3 to 6 months with Lantus® SoloStar®. We have evaluated all available data: sex, age, body mass index, duration of diabetes, complications and associated conditions, treatment before and during Lantus® SoloStar® initiation, insulin dose, as well as the physician's preferred option for improving glycaemic control when needed (e.g. increasing of insulin glargine doses, adding rapid insulin, etc.). There was no specific method for HbA1c determination imposed per protocol.

***Study objectives:*** The primary objective of the study was to evaluate the proportion of patients with HbA1c≤7.0% at the time of survey from the total number of included patients (overall and also separately for T1DM and T2DM patients). We have also collected data about current medical practice (oral antidiabetic drugs association, insulin dosage, basal/rapid insulin ratio).

***Statistical analyses:*** Statistical analyses were performed on the per-protocol population. Statistical testing was performed at a

significance level of α=0.05. Adjusted means and corresponding two-sided 95% confidence intervals (CI) were calculated. The data are presented as mean ± standard deviation values. Student's t-test pairs were used for insulin glargine doses and HbA1c analysis. Statistical analyses were performed using IBM SPSS v20 software.

***Sample size calculation**:* The sample-size was estimated according with the primary end-point assumptions. Presuming a response rate (level of HbA1c<7.0%) of 22% for the glargine-treated patients and estimating from previous trials a percentage of 20% control for non-glargine-treated general diabetic population (data from International Diabetes Management Practice Study), at least 3142 patients should be included in order to attain the primary end-point with an alpha-error level of 5% and a power of 90%.

## Results

From a planned number of 3000 patients we have included 2947 patients, 2946 evaluable, 424 (14.4%) with T1DM and 2522 (85.6%) with T2DM. Diabetes duration was about 8 years. 4.2% (123) patients were diagnosed in the prior year. From the total number of included patients 38.7% were obese, mainly in T2DM. Baseline demographic and clinical characteristics are presented in Table 1.

**Table 1.** Baseline demographics and characteristics of the study population.

| Characteristics | Total | T1DM | T2DM |
|---|---|---|---|
| Number | 2946 | 424 | 2522 |
| Age (yrs.) | 56.5 ± 12 | 40.4 ± 13.4 | 59 ± 10.1 |
| Sex (%) | | | |
| Males | 51.7 | 55.7 | 46.8 |
| Females | 48.3 | 44.3 | 53.2 |
| Diabetes duration (yrs.) | 8.0 ± 6.1 | 9.4 ± 8.3 | 7.7 ± 7.2 |
| Diabetes complications (%) | | | |
| Neuropathy | 3.8 | 3.5 | 4.6 |
| Retinopathy | 4.4 | 5 | 3.6 |
| Renal disease | 3.4 | 2.8 | 3.5 |
| Associated conditions (%) | | | |
| Systemic hypertension | 21.7 | 4.7 | 24.5 |
| Dyslipidemia | 9.3 | 3.3 | 10.3 |
| Peripheral arterial disease | 1.6 | 0.5 | 1.8 |
| Treatment before glargine initiation (%) | | | |
| Oral antidiabetic agents | 69.2 | 4.2 | 80.1 |
| Insulin | 38.2 | 88 | 29.8 |
| Initial dose of glargine (UI) | 22.0 ± 10.9 | 22.0 ± 9.3 | 19.0 ± 9.2 |

***Proportion of patients with HbA1c≤7.0%:*** Over the 3 to 6 months treatment with glargine 37.1% (1092/2946) attained a HbA1c≤7.0%, 11.8 % less than 6.5% (348/2946). In T1DM patients, 35.1% (149/424) attained HbA1c≤7.0%, and 14.6% less than 6.5% (62/424). Similarly, in T2DM, 34.5% (871/2522) attained HbA1c≤7.0%, and 11.3% (286/2522) less than 6.5% (see Figure 1). Mean HbA1c in the total population at inclusion visit (after 3-6 months of glargine treatment) was 7.51% ± 0.99, 7.58% ± 1.15 in T1DM patients, and 7.52% ± 0.95 in T2DM.

***Insulin doses:*** The number of evaluable patients for this analysis was 385 in the T1DM group and 740 in the T2DM group. Insulin glargine dose increased over the 3 to 6 months treatment (from initiation until study inclusion) from a mean daily starting dose of 22.03±10.8 to 26.83±12.5 UI, with a statistically significant

increment of 4.7±7.8 UI (paired sample test, 95% CI). In T1DM the dose increased from 22.9±8.9 to 25.9±9.0 UI and in T2DM from 19.33±9.2 to 25.24±12.1 UI. The difference between the initial and final doses of glargine (calculated only for T2DM) was 5.92±8.8 UI with statistical significance (paired sample test, 95% CI). The final dose represented about 0.33 UI/kg. In patients treated both with basal insulin and rapid insulin, the mean dose for glargine was 26.7 UI in T1DM, with a 0.73 ratio between basal and rapid insulin, whereas in T2DM the mean value was 31.7 UI and the ratio 0.91. Figure 2 presents the distribution of glargine dose correlated with the HbA1c value.

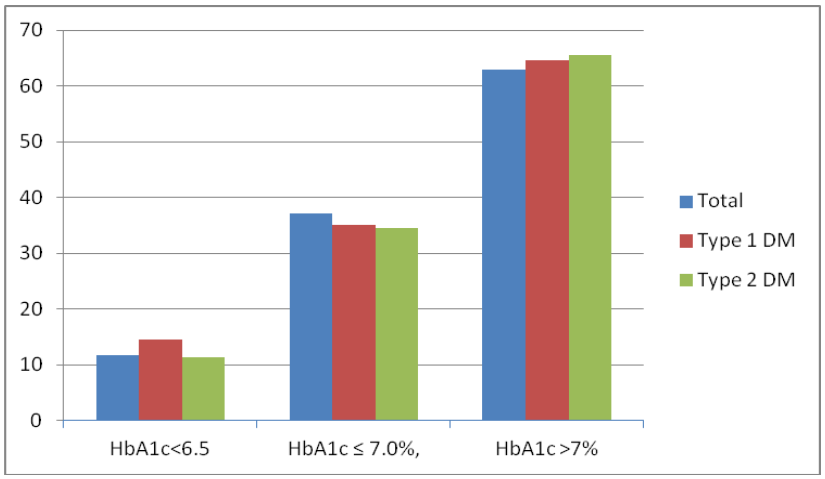


**Figure 1.** The distribution of patients (%) according to HbA1c values.

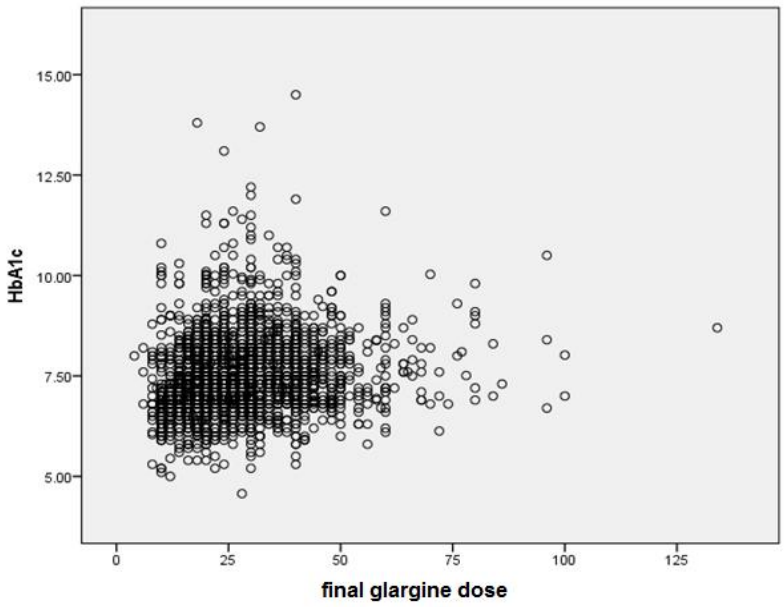


**Figure 2.** The distribution of the final insulin glargine dose correlated with the HbA1c value.

***Physician's options for glycaemic control improvement:*** The physicians' decision for T2DM patients with HbA1c>7% was: to increase the glargine dose in 77.0% of cases (61.5% of the total number of patients), to add prandial insulin in 11.8% (8.6% of the total number of patients) (out of which in 81.5% cases insulin glulizine has been recommended), or to take no action in the rest of the patients.

## Discussion

The primary objective study results show similarity with data reported in the International Diabetes Management Practice Study for Eastern Europe, in which the proportion of patients with HbA1c<7% was 31.3% for T1DM and 36% for T2DM [7]. According to these results, we can consider that Romania is in line with what happens in Europe in terms of glycemic control. Another example is LAUREL-Russia in which only 23% patients had achieved the HbA1c target [10]. If we compare these results with the results obtained with insulin glargine in clinical trials, the proportion of patients that reached HbA1c<7% was 49.4% in the LAPTOP study [9] or 60% in the Treat-To-Target study [6].

Unfortunately, we don't have available data about fasting plasma glucose so we couldn't evaluate if the patients in HbA1c target also have appropriate levels of fasting plasma glucose. This is one of the study limitations together with lack of HbA1c values at Lantus® SoloStar® initiation.

The differences in prescribed mean insulin glargine dose are broad in several studies from 28 [9], to 47 [6] or 68 [11] UI/day. In our study there are some patients that need more than 50 UI/day to achieve glycemic control, but in the same time a high number of patients are still uncontrolled and receive low doses of insulin. In few cases patients are treated with high doses and still remain uncontrolled. In an observational study aimed to investigate the long-term efficacy and safety of adding insulin glargine to support oral antidiabetic treatment in patients with T2DM in everyday practice [12], the insulin glargine dose increased by 5.6 UI over the course of the study, from a mean starting dose of 13.8 ± 6.9 to 19.4 ± 9.1 UI after 9 months (n=11,866). It seems that our final results are comparable with clinical practice from other European countries. However, we consider that an increase of only 5 units of insulin glargine in 3 to 6 months is not in line with current recommendations.

There are no data explaining why some patients fail to achieve good glycemic control during insulin combination therapy. Hypothetically, such failure could be the fault of the health-care professionals (e.g. insufficient advice on titration of insulin doses) or of the patients (e.g. poor adherence, fear of hypoglycemia, inadequate insulin secretory reserve or antibody formation) [11]. It is clear that we need further data in order to better understand the factors that affect reaching the HbA1c target and the decision of stopping titration.

## Conclusions

These results show that in T1DM and T2DM patients treated for 3 to 6 months with Lantus® SoloStar®, the proportion of patients that have reached targets was about 35%. Around 11% of patients had an HbA1c below 6.5%, 14% in T1DM. The mean duration of T2DM until insulin initiation was about 7.7 years.

The dose of insulin glargine, especially in T2DM, was not high (only 0.33 UI/kg), with only a small difference between initiation and 3 to 6 months treatment doses. This could be an indirect proof that in our daily practice there is still the need to reinforce more aggressive basal analogue insulin titration in order to achieve more rapidly the proposed HbA1c target.

We have observed that the ratio between basal and rapid insulin is higher than the recommended one (50% basal and 50% rapid in basal-bolus in type 2 DM) especially in T2DM.

Regarding physician next options for metabolic control improvement, the main one is to increase basal insulin dose and after that to add a prandial insulin.

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